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DEVELOPING BIO-STABLE AND BIODEGRADABLE COMPOSITES FOR TISSUE REPLACEMENT AND TISSUE REGENERATION

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ABSTRACT

Bone is the substantial unit of human skeletal system, which supports the body and its movement. At the ultra-structure level, the bone matrix is a composite material consisting of bone mineral particles, which are mainly substituted, calcium-deficient hydroxyapatite, and collagen, which is a natural polymer. Bone serves as the template for developing bone replacement materials. Research on biomaterials analogous to bone was started in the early 1980s by incorporating bioactive particles into biocompatible polymers so as to produce bone substitutes. Over the last two decades, a variety of bioactive polymer matrix composites have been developed for tissue substitution and tissue regeneration. The bioactive phases in these composites are normally one of the calcium phosphates, especially synthetic hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) which closely resembles bone apatite and exhibits osteoconductivity. If enhanced bioactivity is required, bioceramics having higher bioactivity such as Bioglass® and A-W glass-ceramic can be used as the bioactive phase in the composites. For tissue replacement, bio-stable polymers such as polyethylene (PE) and polysulfone (PSU) are used as the matrix polymer. For tissue regeneration, natural, biodegradable polymers such as polyhydroxybutyrate (PHB) and chitin are used as matrices. Furthermore, mechanical as well as biological performance of a particular composite can be controlled by varying the amount of the bioactive phase in the composite, thus meeting specific clinical requirements. For bioactive ceramic-polymer composites, major influencing factors such as shape, size and size distribution of bioactive particles, mechanical properties and volume percentage of the bioactive phase, properties of the matrix polymer, distribution of bioactive particles in the matrix and the particle-matrix interfacial state should be controlled in order to obtain materials of desirable properties. Various techniques are used to evaluate the composites.

INTRODUCTION

Numerous materials have been used for bone substitution since the 19th century. In modern day orthopaedic surgery, metals such as stainless steel and titanium alloy and ceramics such as alumina and toughened zirconia are common in a variety of implants and devices. However, these materials, having been developed originally for other purposes rather than medical applications, are considerably stiffer than human bone. The modulus mismatch between an implant material and the host tissue can cause bone to resorb at the bone-implant interface, which leads to implant instability and hence eventual failure [1]. A long lasting bone replacement requires the establishment of a stable bone-implant interface, which necessitates the careful matching of the mechanical behaviour as well as properties of synthetic implant materials with the tissue [2]. Furthermore, bone replacement materials must withstand any anticipated physical

loads imposed by body actions without substantial dimensional changes, catastrophic fracture, or failure due to impact, creep, or fatigue within their expected lifetime in the body.

It is now generally recognised that the best material for replacing a body tissue is the one that is similar, if not identical, to that tissue [2]. The advances in composite technology have led to the production of new composites that mimic the structure and match properties of human tissues [3]. These novel materials may overcome problems that have been encountered with the use of conventional implant materials.

STRUCTURE AND PROPERTIES OF BONE

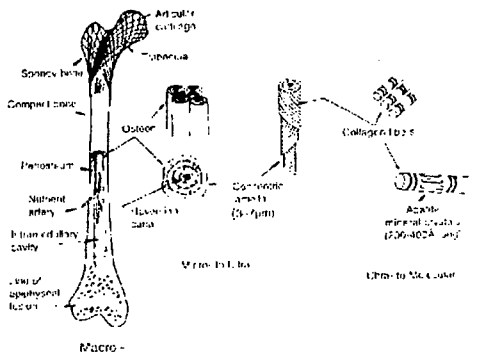

Figure 1 Structural organisation in a human long bone [4]

Bone is the substantial unit of human skeletal system, which supports the body and its movement. Bone, as a natural tissue, has a complex structure in which several levels of organization, from macro- to micro-scale, can be identified [4]. Take a human long bone such as femur for an example (Figure 1). It consists of an outer load-bearing shell of cortical bone with a medullary cavity containing cancellous bone towards the bone ends. Cortical (or compact) bone as a material is anisotropic with osteons (also known as "Haversian systems") being oriented parallel to the long axis of the bone and interspersed in regions of non-oriented bone. Each osteon (about 100 to 300μm in diameter) has a central Haversian canal (20 to 40μm in diameter) containing a blood vessel, which supplies the elements required for bone remodeling. The Haversian canal is surrounded by 4 to 20 concentrically arranged lamellae with each lamella being 3 to 7μm thick. Each adjacent lamellar layer has a different orientation of collagen fibres. Circumscribing the outermost concentric lamella of the osteon is a narrow zone known as cement line, which contains calcified mucopolysaccharides and is devoid of collagen. The cement line is 1 to 2μm thick and is the weakest part of bone. The densely packed concentric lamellae in osteons are composed of two major components: fibrous collagen, which is a natural polymer, and bone mineral. The mineral crystallites that human bone contains are structurally calcium-deficient, carbonate-substituted hydroxyapatite (HA). They are usually refereed to as bone apatite, which normally has dimensions of 5nmx5nmx50nm with a rod-like (or sometimes plate-like) habit and is embedded in collagen fibres. In mature bone, bone apatite occupies about 50% of the total volume. The precise microstructural organization of bone is a function of age and varies between different bones and between different locations of the same bone. Two levels of composite structure are considered when developing bone substitutes: first, the bone apatite

reinforced collagen forming individual lamella (on the nm to μm scale) and, second, osteon reinforced interstitial bone (on the μm to mm scale). It is the apatite-collagen composite at the microscopic level that provides the basis for producing bioceramic-polymer composites for bone replacement.

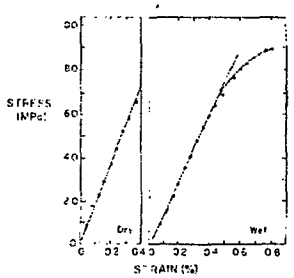

Figure 2 Effect of drying on the behaviour of human cortical bone [5]

Table 1 Mechanical properties of bone and current implant materials [2]

Material	E (GPa)	σ (MPa)	ε (%)	K_{IC} (MN $m^{-3/2}$)
Cortical bone	7-30	50-150	1-3	2-12
Cancellous bone	0.05-0.5	10-20	5-7	
Co-Cr alloys	230	900-1540	10-30	~100
Austenitic stainless steel	200	540-1000	6-70	~100
Ti-6Al-4V alloy	106	900	12.5	~80
Alumina	400	450	~0.5	~3
Hydroxyapatite	30-100	60-190		~1
Polyethylene	1	30	>300	

E : Young's modulus
ε: elongation at fracture
σ : tensile strength (in the case of alumina: flexural strength)
K_{IC} : fracture toughness

The mechanical behaviour of bone may be assessed on whole bones *in vivo*. But the results obtained are difficult to interpret due to irregular shapes of bones and the organizational hierarchy in bones. Normally, mechanical properties of bone (cortical or cancellous) are determined *in vitro* using standard or miniature specimens that conform to various standards originally designed for engineering materials such as metals and plastics. The conditions required to prepare and test dead bone specimens so as to give meaningful results representative of living bone have been well established. It is very important to maintain water content of bone for mechanical assessment as the behaviour of bone in the "wet" condition significantly differs from that of bone in a dry state (Figure 2). In the quasi-static testing condition, a tensile test of "wet" cortical bone at ambient temperature gives a stress-strain curve exhibiting a small viscoelastic component and culminating in brittle fracture at a total strain of 0.5-3.0%. As a result of orientation, location and age, cortical bone has a range of associated properties rather than a unique set of values (Table 1). Young's modulus of bone ranges between 7 and 30GPa. It can also be seen from Table 1 that bone is significantly less stiff than the various alloys and ceramics currently utilized as prosthetic materials, but is stiffer than biomedical polymers. Cortical bone fractures in a brittle fashion, with the ultimate tensile strength being 50 to 150MPa.

It has been shown that fracture toughness, an important parameter for brittle solids, of bone is considerably lower than those of metallic implant materials. The structure and properties of cancellous (or spongy) bone are also well understood and documented [6].

A good understanding of the structure and properties of bone gives structural features and provides the range for approximating mechanical compatibility that is required of a bone analogue material for an exact structural replacement of bone with a stabilized bone-implant interface. It is important to bear in mind, however, that bone is unlike any engineering material in that it can alter its properties and configuration in response to changes in mechanical demand.

BIO-STABLE COMPOSITES

As bone is an apatite-collagen composite material at the ultra-structural level, a polymer matrix composite containing a particulate, bioactive component appears a natural choice for substituting cortical bone. Bonfield *et al* pioneered the use of hydroxyapatite (HA) particles as the bioactive and strengthening phase in polymers to produce bone analogues [7]. Hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) closely resembles bone apatite and exhibits excellent bioactivity. Polyethylene (PE) is a proven biocompatible polymer and hence widely used in orthopaedics. It is therefore natural to combine the two materials to produce a composite that mimics the structure and matches mechanical properties of cortical bone. The ductile polyethylene allows the incorporation of relatively high volume percentages of HA particles in the polymer matrix, which is essential for obtaining bioactivity of the composite. As no other materials are used, all components of the composites are biocompatible.

HA/HDPE composites containing up to 45vol% (i.e. 73wt%) of HA can be routinely made through standardised procedures [8, 9]. The process for manufacturing HA/HDPE composites consists of compounding, powdering (or pelletising) and compression moulding (or injection moulding). Both commercially available HA powders and particulate HA produced in-house have been used to produce HA/HDPE composites. Either a twin screw extruder [8] or an internal mixer [9] was used for compounding the materials efficiently. Powdering of compounded materials usually took place in a centrifugal mill at below -100°C. Compression or injection moulding could produce bulk materials for prostheses or some small medical devices. Composites plates as thick as 20mm could be made by compression moulding. These plates were voids-free, as was revealed by X-ray radiographs.

Rheological studies revealed that the incorporation of particulate HA into HDPE resulted in an increase in the viscosity of composites at their processing temperatures [9]. The presence of the HA particles restricted molecular mobility of HDPE under shear and hence resulted in higher viscosity. This increase in viscosity was more pronounced at low shear rates. With an increase in shear rate, the viscosity of HA/HDPE composites approached that of the unfilled HDPE. Both HDPE and HA/HDPE composites showed pronounced shear thinning behaviour. HA/HDPE composites at their processing temperatures exhibited discontinuity with a varying shear rate. As the HA content in the composites increased, the shear rates at which discontinuity occurred were reduced. The die swell ratio of HA/HDPE composites was reduced as the HA content was increased. It is possible that the presence of HA particles in the polymer matrix reduced the degree of recoiling of the HDPE molecular chains and hence led to the reduction in swelling of composites. Analysis of rheological behaviour of HA/HDPE composites is important for optimising composite processing conditions and for producing high quality net-shape (or near near-shape) devices.

SEM examinations of polished HA/HDPE surfaces showed that after the compounding process, HA particles were well dispersed, exhibiting a homogeneous distribution in the polymer matrix (Figure 3). Subsequent composite processing by compression moulding or injection moulding preserved these characteristics. This uniform distribution of HA particles in composites is essential for mechanical as well as biological performance of implants. Using the image analysis technique and stereology, it was possible to calculate the average volume diameter of HA particles in composites from SEM micrographs (i.e., from two-dimensional images to three-dimensional projections). The calculations indicated that the high shear forces generated during the compounding process broke up HA particle agglomerates into unit particles in the polymer matrix [10]. The average volume diameter of HA particles in compounded HA/HDPE was nearly the same as the mean particle size of HA powder used for producing the composites. SEM examinations of tensile fracture surfaces suggested that in the composites there was only mechanical bond between HA particles and HDPE matrix resulting from the shrinkage of HDPE around individual HA particles during thermal processing [8,11].

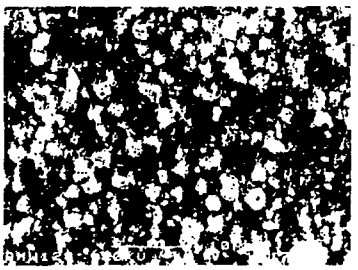

Figure 3 Uniform distribution of HA particles in HA/HDPE composite containing 40vol% of HA [8]

It was found that compounding caused slight decreases in the weight average molecular mass (M_w) of HDPE, with the decrease being dependent on the HA volume percentage [11]. Further thermal processing by compression or injection moulding also reduced M_w. Differential scanning calorimetry (DSC) results indicated that the addition of HA particles caused decreases in the degree of crystallinity of HDPE, with composites of higher HA contents having lower degrees of crystallinity for the polymer matrix [12].

Thermogravimetric analysis (TGA) was used to determine the real HA content in HA/HDPE composites. Calculations made from TGA curves showed that the difference between the actual mass percentages of HA in the composites produced and the "Rule of Mixtures (ROM)" values was negligible and hence the intended compositions had been achieved [9, 12].

By varying the amount of HA in the composites, a range of mechanical properties of the composites could be obtained. An increase in the HA volume percentage led to increases in the Young's modulus, shear modulus and tensile strength of HA/HDPE, with a corresponding decrease in the strain to fracture [8, 13]. The particle morphology and average particle size of HA were found to affect mechanical properties of HA/HDPE composites [13]. HA/HDPE with 45vol% of HA possessed a Young's modulus value of 5.54GPa, which approaches the lower bound for cortical bone (Table 2). HA/HDPE composites containing 40vol% or more of HA appeared to be suitable for bone substitution, with the actual composite to be used being dependent on the nature of bone being replaced and the applied physiological load.

Table 2 Mechanical properties of HA/HDPE composites and cortical bone

HA Volume (%)	E (GPa)	G (GPa)	σ (MPa)	ε (%)
0	0.65±0.02	0.28±0.10	17.89±0.29	>360
10	0.98±0.02	0.39±0.16	17.30±0.27	>200
20	1.60±0.02	0.48±0.07	17.77±0.09	34.0±9.5
30	2.73±0.10	0.71±0.17	19.55±0.20	6.4±0.5
40	4.29±0.17	1.18±0.07	20.67±1.56	2.6±0.4
45	5.54±0.62	1.46±0.26	18.98±2.11	1.9±0.2
Cortical bone*	7-30	~3.2	50-150	1-3

E : Young's modulus G : shear modulus σ : tensile strength ε: elongation at fracture
* E, σ and ε values from Ref.2; G value from Ref.14.

The creep behaviour of HA/HDPE composites was investigated using a three-station tensile creep machine [15, 16]. The inclusion of HA particles in HDPE improved the short-term creep resistance when specimens were subjected to similar stresses, and an increase in the HA volume percentage increased creep resistance. However, creep failure of composites could occur at long times due to debonding at the HA-HDPE interface. The immersion in Ringer's solution reduced the creep resistance of HA/HDPE composites. The decrease in creep resistance was found to be a function of HA volume percentage [16]. This effect was due to the penetration of fluid into the composites.

Biaxial (i.e., axial and torsional) fatigue tests were conducted for HA/HDPE composites [17]. A fixed axial component of 50% of ultimate tensile strength (UTS) with the torsional component varying from 0% to 50% of ultimate shear strength (USS) was used for fatigue tests. Generally, the fatigue life of HDPE and the composites was reduced with an increasing shear stress in the biaxial stress condition. The addition of particulate HA in HDPE led to shorter fatigue life in low shear stress conditions. In high shear stress conditions, the effects of shear stress became dominant and the fatigue life of both HDPE and HA/HDPE was about the same.

Tribological properties of HA/HDPE composites were evaluated against duplex stainless steel under dry and lubricated conditions [18]. Lubricants used were distilled water and aqueous solutions of proteins (egg albumen or glucose). HA/HDPE composites appeared unsuitable for implants with articulating surfaces due to the formation of an abrasive slurry of HA in the lubricants.

The biological performance of implant materials can be evaluated by *in vitro* tests, using simulated body fluid or cell cultures, or by *in vivo* assessments. In *in vitro* experiments using human osteoblast cell primary cultures, it was observed that the osteoblast cells attached to "islands" of HA in the composites and subsequently proliferated, which clearly showed the biocompatibility and bioactivity of HA/HDPE composites [19].

For *in vivo* experiments, following sterilization by γ irradiation, machined pins (Φ2.4mmx5mm) of HA/HDPE composites were implanted in the lateral femoral condyle of adult New Zealand white rabbits [20]. It was demonstrated that cortical and cancellous bones responded positively to the presence of HA/HDPE implants by localized apposition adjacent to the implant surface. After six month implantation, the areas of direct bone apposition, as measured from histological sections, had reached 40% of the implant surface. The mechanical compatibility of the HA/HDPE composite with natural bone had resulted in the absence of significant relative movement at the bone-implant interface, thus encouraging bone growth

around the implant. Ultra-microtomed specimens were prepared for the TEM examination of the bone-implant interface [21]. At one month, the new bone was mainly seen adjacent to the interface where HA particles were present. At six months, the bone tissue was seen growing along the whole length of composite implant including exposed HA particles and polyethylene matrix. The image of lattice planes at the bone-implant interface after three months implantation is shown in Figure 4, exhibiting continuity across the interface and thus indicating epitaxial growth of apatite crystals from the implant.

Figure 4 High resolution TEM image of the bone-implant interface for a HA/HDPE implant (The interface between the bone region B and composite C is marked with arrows.) [21]

Since the late 1980s, subperiosteal orbital floor implants made from HA/HDPE composites have been used in the correction of volume deficient sockets and in orbital floor reconstruction following trauma [22, 23]. All the implants remained in position and no infection or extrusion occurred. Clinical examinations found the implants to feel stable. After six months implantation, computer tomography (CT) was unable to detect any gap between the implant and the bone, implying at least partial integration of the implant with the orbital floor, which accounted for the marked implant stability. More recently, middle ear implants were made from HA/HDPE composites and satisfactory clinical results have been obtained [24].

To improve mechanical properties of HA/HDPE composites for load bearing implant applications, hydrostatic extrusion of the composites was investigated [25]. It was found that higher extrusion ratios led to higher Young's modulus and tensile strength of HA/HDPE composites which are inside the bounds for mechanical properties of cortical bone. The fracture strain of HA/HDPE was also substantially increased by hydrostatic extrusion. Hydrostatically extruded HA/HDPE containing 40vol% of HA possessed a strain to fracture which was far greater than that of human cortical bone (9.4% vs. 1-3%). Furthermore, the bioactivity of the composites was retained after extrusion. Therefore, HA/HDPE further processed via hydrostatic extrusion exhibits great potential for major load bearing applications. An alternative method to enhance mechanical properties of the composites, i.e., using coupling agents for the composites, was also investigated [26]. However, only marginal improvements were achieved.

Apart from polyethylene, there are a few other biomedical polymers that could be used for producing bone analogue materials. Polysulfone (PSU) is an amorphous polymer which possesses high specific strength and modulus. To develop bioactive composites for load bearing prostheses, PSU may be a better choice for the matrix of a composite than HDPE as its strength and modulus are significantly higher [27], which can provide a higher baseline for composite properties. Other favourable properties of PSU are low creep rate, resistance to oxidation, excellent resistance to hydrolysis or reduction of molecular weight, stability in aqueous inorganic acids, alkalis and salt solutions, and bioinertness. Furthermore, PSU has high resistance to β-, γ-, X- and IR-radiation and can be steam-sterilised. Therefore, HA/PSU composite has been

developed as a new tissue replacement material [28]. The production of HA/PSU composite followed the same procedure as that for manufacturing HA/HDPE composites [9]. HA/PSU composite containing up to 40vol% of HA was produced. HA particles were also well dispersed in the PSU matrix. Thermogravimetric analysis (TGA) verified the amount of HA in the composite. Density close to the theoretical value was achieved for the composite, indicating a void-free structure. Rheological analysis revealed that PSU and the composite exhibited pseudoplastic flow behaviour at processing temperatures. With an increase in HA content, stiffness of HA/PSU composite also increased. Mechanical properties of HA/PSU composite are within the lower bound for bone. Just as for the HA/HDPE composites, in biaxial fatigue testing, the torsional stress significantly reduced the fatigue life of HA/PSU composite [17].

In order to establish a stronger implant-bone bond within a shorter period of time, glass or ceramics that are more bioactive than HA, such as Bioglass® and A-W glass-ceramic, could be used as the bioactive phase in composites. Bioglass® is a family of bioactive glasses that elicit specific physiological responses, including the provision of surface-reactive silica, calcium and phosphate groups, and alkaline pH levels, at interfaces with tissues. A particular advantage of Bioglass® is its ability to bond to both hard and soft tissues. A-W glass-ceramic has excellent mechanical properties while possessing good bioactivity. Using the technology for HA/HDPE composites, Bioglass® or A-W glass-ceramic reinforced polyethylene composites were produced [29, 30]. It was found that Bioglass® particles were well dispersed and a reasonably homogeneous distribution of the particles in the polymer matrix was achieved. Composite with up to 30vol% of Bioglass® exhibited levels of elastic compliance, tensile strength and fracture strain comparable to those of soft connective tissues. Composite with Bioglass® volumes in excess of 30vol% possessed mechanical properties comparable to cancellous bone. In *in vitro* experiments, osteoblast cells were found to attach to Bioglass® particles in the composite (Figure 5), indicating excellent biocompatibility and bioactivity of the composite.

Figure 5 Osteoblast cells attaching to Bioglass® particles in the Bioglass® /HDPE composite [19]

BIODEGRADABLE COMPOSITES

In recent years, emphasis in biomaterials engineering has moved from materials that remain stable in the biological environment to materials that can alter their properties (i.e., "biodegrade") in response to the cellular environment. Biodegradable materials are designed to degrade gradually in the body and will be replaced eventually by newly formed tissues. After implantation in the body, a biodegradable bone substituting material will have gradual decreases in strength and stiffness over a clinically determined optimal period. As bone repairs itself, the

natural polymer is biodegradable due to its β-1,4 glycosidic linkages being susceptible to the lysozyme present in the human body. HA/chitin composite could be produced using the solution casting technique, with a homogeneous distribution of HA particles in the composites being achieved [33]. The solution casting process did not change the crystalline structure of chitin. TGA results indicated that intended compositions were achieved for the composite. Tensile testing results revealed that the strength and modulus of HA/chitin composite decreased with an increase in the amount of particulate HA in the composite. SEM examination of fracture surfaces showed that HA particles were separated from the chitin matrix completely after tensile tests. These results suggested that there was no chemical bond between the two constituents of the composite. *In vitro* mineralisation experiments showed that HA particles rendered the composite bioactive and significantly improved the ability of composites to induce the formation of bone-like apatite on their surfaces. Degradation of chitin in the simulated body environment was observed.

SUMMARY

Using body tissues as templates, various bioactive ceramic-polymer composites have been developed over the last two decades for tissue replacement and tissue regeneration. Each of these composites has its distinctive characteristics and may be used in specific clinical situations. Bio-stable composites have gained success for tissue replacement. Biodegradable composites appear to provide the best biomaterials solution for tissue substitution and there is still a large scope for developing this type of composites. The advances in materials science and technology certainly aid in further research into bioactive composites for medical applications.

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